Letter to the Editor

Effects of Seasonal and Temperature Variations on the Association between Nitrogen Dioxide Exposure and First-Aid Incidence for Neurological Diseases in Shenzhen, China*

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Neurological disorders, including headaches (tension-type headaches, medication-overuse headaches, and migraines) and dementias that include Alzheimer's disease, are among the most prevalent and debilitating global conditions. In 2016, these disorders affected 276 million people worldwide and were the second leading cause of death that year[1]. This highlights the urgent need for effective prevention, treatment, and support strategies. The etiology of neurological disorders is multifaceted and involves genetic, environmental, physiological, and social factors[2].

Recent studies have identified ambient air pollution as a major risk factor for neurological disorders. For instance, research conducted on a Canadian urban population demonstrated a link between ambient air pollution and an increase in emergency department visits for neurological disorders, particularly paroxysmal diagnoses[3]. Additionally, both extremely high and low temperatures contribute to increased mortality owing to neurological disorders. Temperature often acts as a confounding factor in studies examining the health effects of air pollution, and vice versa.

The synergistic effects of the ambient temperature and air pollution on neurological conditions remain poorly understood. Existing research has primarily focused on individual neurological conditions and produced inconsistent results. Comprehensive studies of the combined effects of ambient temperature and air pollution on a broad range of neurological disorders are limited.

This study aimed to assess whether ambient temperature modifies the effects of nitrogen dioxide (NO_2) on first-aid for neurological disorders. A subgroup analysis sought to identify sensitive populations.

Shenzhen, located in the Pearl River Delta region with a low-latitude subtropical monsoon climate, is a densely populated first-tier city, making it an ideal location for studying the interactions between NO_2 and temperature, considering its population characteristics, geography, and urban development.

Data on daily first-aid cases between 01 January 2013 and 31 December 2020 were provided by the Shenzhen Center for Disease Control and Prevention. We extracted individual-level data for the neurological disease outcome groups (G00–G99) according to the International Classification of Diseases, 10th revision. First-aid records were categorized according to sex and age (individuals < 65 and ≥ 65 years of age).

Data on air pollutants, including NO_2, inhalable particulate matter ($PM_{2.5}$ and PM_{10}), and sulfur dioxide (SO_2), were collected from seven environmental monitoring stations located in different administrative districts of Shenzhen. The Shenzhen Meteorological Service Centre provided

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meteorological information on temperature and humidity. The data included daily average values of temperature and relative humidity. These values were calculated as the average of four values based on hourly measurements taken at 02:00, 08:00, 14:00, and 20:00 h each day to ensure a comprehensive representation of the daily meteorological conditions. Temperatures were stratified into high and low levels, with the cutoff value defined as the median temperature[4]. The cold and warm seasons were defined as the periods from November to April and from May to October, respectively[5].

Based on previous studies on neurological disorders and air pollutants, we expected the impact of air pollutants on neurological disorders to persist for approximately one week[6]. Accordingly, we employed the following quasi-Poisson regression model to control for overdispersion:

$$\log[E(Y_t)] = \alpha + \beta NO_{2t,l} + ns(Time, df) + ns(Temp, 3) + ns(Humid, 3) + \gamma Holiday + \gamma DOW \quad (1)$$

where $E(Y_t)$ represents the expected number of emergency cases at a time (variable t); α is the intercept; $\beta NO_{2t,l}$ signifies the cross-basis constructs designed to calculate the linear effects of air pollutants; l is the number of lag days; β is the coefficient vector for $NO_{2t,l}$.

A natural cubic spline function was utilized to capture lag effects, and a linear function was adopted to depict the exposure-response trajectory for the correlation between air pollutants and the occurrence of first-aid cases. In the above-mentioned equation, ns (Temp, 3) and ns (Humid, 3) represent natural spline functions indicating the intraday temperature and humidity, respectively; DOW denotes the day of the week with its regression coefficient γ; Holiday is a binary variable indicating a public holiday.

To compare the relative influence of air pollutants, we quantified the rise in the number of first-aid instances for neurological diseases as the percentage increased, which was calculated using the formula (RR-1) ×100% for every 10 μg/m^3 increase in NO_2 concentration.

Parametric stratification models were integrated with generalized additive models to estimate the interactive effects of NO_2 and temperature on neurological disorders. To analyze the lag effects of NO_2, we employed a moving average approach, considering that the effects of NO_2 typically persist for several days. Using a moving average, lag effect (lag0–2, lag0–4, and lag0–6) was deemed appropriate for capturing the lagged effect. The formula for this model is as follows:

$$\log[E(Y_t|X)] = \alpha + \beta_1 NO_2 + \beta_2 Temp_k + \beta_3(NO_2 : Temp_k) + ns(Time, df) + ns(Temp, 3) + ns(Humid, 3) + \gamma Holiday + \gamma DOW \quad (2)$$

where $Temp_k$ represents the temperature on the current day, β_1, β_2 and β_3 denote the main effects of NO_2 and ambient temperature on neurological disorders and the interactive effects of the two factors, respectively. The estimated effects of NO_2 on days with low temperature can be denoted as β_1, while $\beta_1 + \beta_3$ represents the effects of NO_2 on days with high temperature.

To estimate the covariance intervals, we used a method incorporating pollutant coefficients, pollutant covariance, and interaction terms, expressed as:

$$\widehat{Q}_1 - \widehat{Q}_2 \pm \sqrt{\widehat{SE}_1^{\,2} + \widehat{SE}_2^{\,2}} \quad (3)$$

where $\widehat{Q}_1$ and $\widehat{Q}_2$ are the estimates of the two categories and $\widehat{SE}_1$ and $\widehat{SE}_2$ are their respective standard errors.

To test the stability of the seasonal adjustment models, sensitivity analyses of ambient air pollution were performed by varying the maximum number of lag days of ambient air pollution. To mitigate the potential confounding effects of other ambient pollutants, additional co-pollutants were incorporated into both the seasonally stratified and temperature-stratified models. This enabled the fitting of a two-pollutant model, thus addressing the potential confounding effects. To prevent bias from the possible prolonged effects of cold temperature on the nervous system, a 14-day moving average and cross-lagged nonlinear treatments were applied to the models in seasonal stratification. The cutoff values for temperature stratification were adjusted accordingly. We included a binary variable in our model to indicate whether the period was affected by the pandemic, defining 23rd January 2020 to 31st December 2020 as the pandemic period.

All analyses were performed using R version 4.2.2 with the dlnm and mgcv packages.

Table 1 displays data on environmental

Table 1. Summary statistics for air pollution, weather parameters, and first-aid volume of neurological diseases stratified by season and temperature in Shenzhen, 2013–2020

Variables	Sum	Min	P_{25}	*M*	P_{75}	*Max*	*x*	*s*	IQR
Weather parameters									
Mean temperature (°C)									
Full year		3.50	19.60	24.70	28.10	33.00	23.55	5.30	8.50
Cold season		3.50	16.60	19.60	22.40	28.00	19.30	4.03	5.80
Warm season		18.80	26.50	28.10	29.40	33.00	27.76	2.09	2.90
Low temperature		3.50	16.60	19.60	22.20	24.60	19.10	3.76	5.60
High temperature		24.70	26.60	28.10	29.40	33.00	27.97	1.68	2.80
Relative humidity (%)									
Full year		19.00	70.00	78.00	84.00	100.00	75.73	12.88	14.00
Cold season		19.00	65.00	75.00	83.00	100.00	72.63	14.55	18.00
Warm season		34.00	73.00	80.00	86.00	100.00	78.80	10.09	13.00
Low temperature		19.00	64.00	74.50	83.00	100.00	72.09	14.99	19.00
High temperature		39.00	74.00	80.00	85.00	100.00	79.35	9.03	11.00
Daily air pollutant components NO_2 (μg/m^3)									
Full year		6.73	23.73	31.40	41.11	139.40	34.46	16.17	17.38
Cold season		9.55	26.98	35.23	48.00	139.40	39.42	18.49	21.02
Warm season		6.73	21.16	27.71	35.87	83.80	29.55	11.56	14.71
Low temperature		9.55	26.45	35.25	48.00	139.40	39.24	18.58	21.55
High temperature		6.73	21.45	28.00	35.83	83.80	29.72	11.55	14.38
Daily onset counts									
All									
Full year	79,853	4	19	25	35	69	27	11	16
Cold season	38,608	4	18	24	34	69	27	11	16
Warm season	41,245	5	20	26	35	64	28	11	15
Low temperature	38,784	4	18	24	34	69	27	11	16
High temperature	41,069	5	20	26	35	64	28	11	15
Female									
Full year	32,216	0	7	10	14	31	11	5	7
Cold season	15,487	0	7	10	14	31	11	6	7
Warm season	16,729	0	7	11	15	30	11	5	8
Low temperature	15,563	0	7	10	14	31	11	6	7
High temperature	16,653	0	7	11	14	30	11	5	7
Male									
Full year	47,622	2	11	15	21	40	16	7	10
Cold season	23,114	2	11	15	20	40	16	7	9
Warm season	24,508	3	12	16	21	38	17	7	9
Low temperature	23,212	2	11	15	20	40	16	7	9
High temperature	24,410	3	12	16	21	38	17	7	9

Continued

Variables	Sum	Min	P_{25}	*M*	P_{75}	*Max*	*x*	*s*	IQR
Age < 65 years									
Full year	69,270	3	17	23	30	56	24	9	13
Cold season	32,966	4	16	22	28	56	23	9	12
Warm season	36,304	3	18	24	31	56	25	9	13
Low temperature	33,106	4	16	22	28	56	23	9	12
High temperature	36,164	3	18	24	31	56	25	9	13
Age ≥ 65 years									
Full year	10,583	0	1	3	5	21	4	3	4
Cold season	5,642	0	1	3	5	21	4	4	4
Warm season	4,941	0	1	2	5	17	3	3	4
Low temperature	5,678	0	1	3	5	21	4	4	4
High temperature	4,905	0	1	2	5	17	3	3	4

Note. NO_2, nitrogen dioxide; Sum, total number; Min, minimum; *M*, median; *Max*, maximum; *s*, standard deviation; *x*, daily mean temperature; IQR, interquartile range.

pollutants, meteorological conditions, and the daily incidence of emergencies related to neurological diseases in Shenzhen between 2013 and 2020. The average number of daily first-aid cases per year was 25. The average values for the cold and warm seasons were 24 and 26, respectively. The average temperature values for the two temperature levels were 24 °C and 26 °C, respectively. The average concentration of NO_2 was 39.42 and 29.55 μg/m^3 during the cold and warm seasons, respectively. Considering the median daily air temperature of 24.70 °C, NO_2 concentrations in the low- and high-temperature layers were 39.24 and 29.72 μg/m^3, respectively. Additional statistical characteristics are presented in Table 1.

The percentage increase in neurological disease emergencies due to NO_2 concentrations surpassed zero for each single-day lags (lag0–6) throughout the year (Figure 1). During the cold season, the percentage increase in first-aid cases owing to NO_2 concentrations exceeded that during the warm season. This increase was particularly notable in the female and elderly groups, mainly at short-term lags (lag0 and lag1). Conversely, during the warm season, the observed percentage increase was marginally above 0 in the overall population, with the male group and those < 65 years of age exhibiting significant effects at single-day lags (lag2, lag3, and lag4); the rest showed no significant effects. Females and young adults were at a higher risk of exposure than the other groups. Studies have explored sex-based differences in neurological disorders from a physiological standpoint. For instance, exposure to sex-specific events, such as pregnancy, has been linked to an increased risk of a certain type of multiple sclerosis[7]. In contrast to the findings of most previous studies, we found that younger individuals were more susceptible to NO_2 pollution during low temperature conditions and cold seasons than were older individuals (≥ 65 years). Young people often spend more time outdoors, thereby increasing their exposure to unfavorable factors such as air pollution.

We investigated the seasonal stratification of the effects of ambient air pollutants, focusing on the cumulative percentage increase in first-aid cases for neurological diseases. As shown in Table 2, throughout the period of one year, the effect of NO_2 was significant in all populations and subgroups of lag0–2, lag0–4, and lag0–6, except for lag0–4 and lag0–6 in those ≥ 65 years of age. The effects of NO_2 during the cold season resulted in a significant increase in the number of neurological disease emergencies than that during the warm season for the total population as well as for both the sex subgroups in all lag periods. Seasonal analysis showed that elevated NO_2 concentrations were positively correlated with the number of neurological emergencies. Additionally, we observed a significant impact of air pollution on the onset of neurological diseases in winter.

To more comprehensively assess this relationship, we stratified the temperature to investigate the interaction between NO_2

concentration and temperature on first-aid rates for neurological diseases. A temperature-stratified model was used to assess the effects of pollutants at different temperatures. Table 2 presents the estimated effects of NO_2 on the number of first-aid sessions for neurological diseases on low-temperature days. The differences between low and high temperatures were statistically significant at moving average lags of lag0–2, lag0–4, and lag0–6 days. For instance, for all individuals, with each 10 μg/m^3 increment in NO_2 concentration, the instances of first-aid for neurological diseases increased by 4.43% (95% *CI*: 3.30, 5.57) on low-temperature days and by 1.47% (95% *CI*: –0.12, 3.08) on high-temperature days. Subgroup analysis revealed that the effects of NO_2 on the number of first-aid sessions

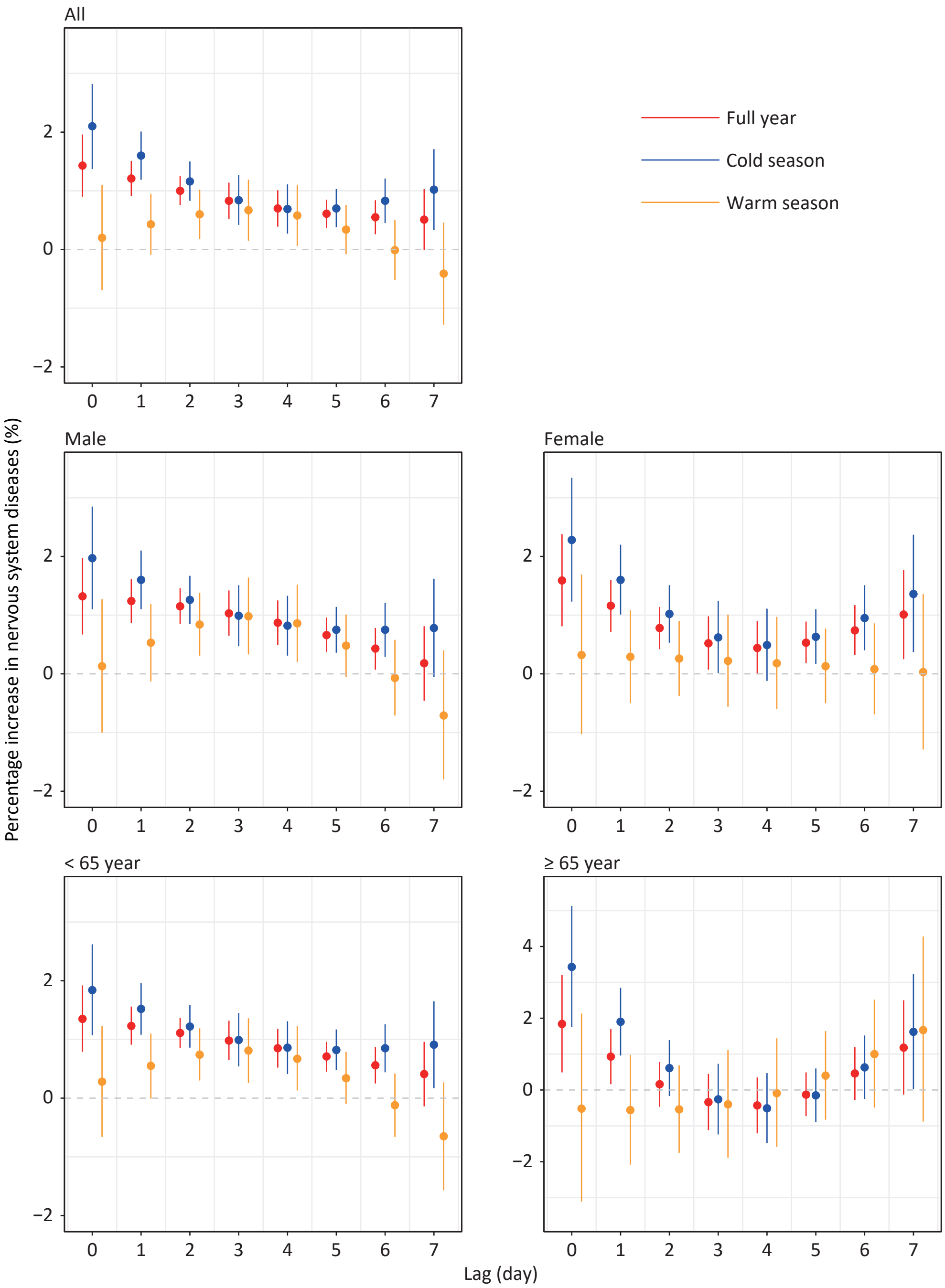

Figure 1. Distributed lag analysis of seasonal-adjusted NO_2 impacts on neurological emergencies per 10 μg/m^3 rise.

for neurological diseases were higher on low-temperature days in women and youn people than those in men and older individuals (≥ 65 years), respectively. Consistent with the results of seasonal analyses, we observed that the effect of NO_2 on neurological diseases was more pronounced on low-temperature (≤ median temperature) days than on high-temperature days. There are several possible mechanisms for the relationship between ambient temperature and air pollutants. First, cold stress may induce glial cell activation, neuroinflammation, and neuronal damage, as demonstrated in the hippocampus[8]. Moreover, NO_2 inhalation can increase the levels of the c-fos and c-jun oncogenes and the expression of the p53, bax, and bcl-2 apoptosis-related genes, induce neurotoxicity, and

Table 2. Percentage increase (95% *CI*) in the firstaid volume of neurological diseases for each 10 μg/m^3 increment in NO_2 concentrations by season and temperature in Shenzhen, 2013–2020

Group	Season/temperature	Percentage increase in death (95% *CI*)[b]		
		Lag0–2	Lag0–4	Lag0–6
All[a]	Full year	3.68 (2.74, 4.63)*	5.27 (4.16, 6.39)*	6.50 (5.27, 7.74)*
	Cold season	4.94 (3.64, 6.25)†	6.55 (5.02, 8.12)†	8.20 (6.50, 9.92)†
	Warm season	1.23 (0.36, 2.85)	2.50 (0.60, 4.44)	2.83 (0.67, 5.04)
	Low temperature	4.43 (3.30, 5.57)†	5.40 (4.06, 6.75)†	6.22 (4.70, 7.77)†
	High temperature	1.47 (0.12, 3.08)	2.52 (0.67, 4.41)	3.02 (0.97, 5.10)
Female	Full year	3.57 (2.19, 4.97)*	4.57 (2.95, 6.22)*	5.91 (4.11, 7.74)*
	Cold season	4.99 (3.11, 6.89)†	6.16 (3.95, 8.43)†	7.85 (5.40, 10.35)†
	Warm season	0.88 (1.53, 3.35)	1.29 (1.57, 4.22)	1.50 (1.75, 4.87)
	Low temperature	5.04 (3.47, 6.63)†	5.82 (3.97, 7.71)†	6.97 (4.86, 9.13)†
	High temperature	0.04 (2.13, 2.27)	0.19 (2.72, 2.40)	0.26(2.53, 3.13)
Male	Full year	3.76 (2.61, 4.93)*	5.75 (4.38, 7.13)*	6.90 (5.39, 8.43)*
	Cold season	4.90 (3.34, 6.48)†	6.80 (4.94, 8.70)†	8.41 (6.36, 10.50)†
	Warm season	1.50 (0.52, 3.57)	3.38 (0.96, 5.87)	3.81 (1.04, 6.64)
	Low temperature	4.71 (3.34, 6.10)†	5.97 (4.37, 7.60)	6.85 (5.04, 8.70)
	High temperature	2.07 (0.10, 4.07)	3.83 (1.54, 6.17)	4.33 (1.82, 6.91)
< 65 years	Full year	3.74 (2.74, 4.76)*	5.65 (4.47, 6.85)*	6.99 (5.68, 8.32)*
	Cold season	4.65 (3.27, 6.06)†	6.60 (4.95, 8.28)†	8.39 (6.57, 10.24)†
	Warm season	1.58 (0.12, 3.30)	3.09 (1.06, 5.16)	3.31 (1.01, 5.67)
	Low temperature	5.47 (4.27, 6.68)†	7.00 (5.59, 8.43)†	8.10 (6.50, 9.72)†
	High temperature	2.22 (0.52, 3.94)	3.71 (1.74, 5.72)	4.23 (2.07, 6.44)
≥ 65 years	Full year	2.95 (0.58, 5.36)*	2.15 (0.58, 4.97)	2.49 (0.53, 5.60)
	Cold season	6.03 (3.05, 9.09)†	5.22 (1.74, 8.81)†	5.72 (1.91, 9.67)
	Warm season	1.61 (6.14, 3.13)	2.09 (7.39, 3.51)	0.72 (6.86, 5.82)
	Low temperature	2.92 (0.22, 5.70)	1.71 (1.42, 4.94)	1.98 (1.51, 5.60)
	High temperature	0.67 (4.93, 3.78)	0.99 (5.88, 4.16)	1.37 (4.12, 7.17)

Note. NO_2, nitrogen dioxide; *CI*, confidence interval; Temp, temperature; [a]"All" means daily death count, not stratified by sex or age; [b]Estimates were generated using a distributed lag linear model, adjusted for calendar day [natural cubic spline with 5 degrees of freedom (*df*)for full year and 3 *df* for seasonal analysis], day of the week, holiday, temperature (lag0, natural smooth function, 3 *df*), and humidity (lag0, natural smooth function, 3 *df*). We used a sevenday lag distributed linear model to examine the lag effect of NO_2 on mortality; *Statistically significant at the 5% level of significance (P < 0.05); †*Z* test for the difference between the two relative risks of subgroup analysis results at the 5% level of significance (P < 0.05).

cause various neurological disorders[9]. Inflammation and oxidative stress are the two main processes through which air pollutants exert toxic effects on the central nervous system[10]. The two processes are linked, and this common mechanism may be responsible for the synergistic effect.

The sensitivity analyses conducted using various NO_2 lag days (Supplementary Table S1, available in www.besjournal.com) revealed consistent seasonal effects. Adjustment for temperature (Supplementary Table S2, available in www.besjournal.com) revealed varying effects on the male population throughout the year, and among individuals, it varied by age during the cold season. However, the effect on the total population remained unchanged. The effect of NO_2 on neurological diseases did not change significantly (except for the male group at lag0–2) when different ambient temperatures were chosen as the cutoff points for the temperature-stratified models (Supplementary Table S3, available in www.besjournal.com). The addition of co-pollutants to our model did not significantly alter the rate of first-aid due to onset of neurological disorders in either of the seasonal or temperature models (Supplementary Tables S4–S5, available in www.besjournal.com). The addition of variables representing the epidemic measure in the model showed that the significance of the impact of NO_2 concentration on neurological diseases in both the cold and warm seasons remained unchanged (Supplementary Table S6, available in www.besjournal.com).

This study has some limitations. First, we obtained only ambient pollutant data from environmental monitoring stations with information on first-aid on the day, lacking individual measurements. Moreover, air pollutant data were collected at different monitoring stations, potentially leading to variability in measurements. Spatial heterogeneity existed between air pollutant measurements and meteorological factors, highlighting the need to incorporate personal geographical information to obtain reliable results. Second, our study focused on Shenzhen, limiting its generalizability to other regions because of the differences in climatic conditions, geographic topography, and demographics. Third, our study was limited to a broad category of neurological disorders and did not break down the effects of these factors more specifically for subspecies of disorders. In future studies, we aim to improve the data collection methods to include individual-level exposure measurements. This would help provide a more precise assessment of the health effects of pollution and reduce potential bias. In addition, more detailed data and subgroup analyses are needed based on the severity, origin, and chronicity of the disorder. This information would provide a more comprehensive understanding of the specific impacts of air pollution on various neurological conditions.

Our study revealed that cold seasons and low temperatures significantly modified the effects of NO_2 on neurological disorders, with women and young people exhibiting greater susceptibility to cold weather conditions than those in men and older individuals (≥ 65 years), respectively. Prioritizing the health effects of extreme weather on susceptible populations and implementing appropriate measures are crucial steps towards reducing the health burden caused by temperature and air pollution in synergy.

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